Drug induced liver injury (DILI) is a clinical entity that is the leading cause of drug withdrawal from the market and discontinuation of clinical drug development plans, and remains the most common cause of acute liver failure (ALF) in the west (1). Conventionally, it has been classified into intrinsic and idiosyncratic forms. The former is usually predictable, dose-dependent, and reproducible in pre-clinical experimental models, while the latter is largely unpredictable, falling short of any known pharmacological characteristic of the drug in question, and mostly cannot be explained by animal toxicology studies (2).

In stark contrast to intrinsic DILI, the diagnosis of idiosyncratic DILI remains fraught with uncertainty and is the most problematic. Risk factors that may predispose to developing DILI include an older age, female gender, concurrent drugs, comorbidity and genetics (2). Clinical presentation and course are indistinguishable from other common hepatic disorders, and pre-existing liver diseases, comorbid conditions and polypharmacy can be potent confounders. Symptomatology may be variable, from subclinical disease with elevated liver function tests, to cholestasis, acute fulminant hepatitis, or sinusoidal obstruction syndrome (3), and thorough investigative workup may be required to exclude other potential causes such as viral hepatitis, autoimmune hepatitis etc.

In the United States, some of the most frequently encountered drugs causing idiosyncratic DILI include antimicrobials (amoxicillin-clavulanate, nitrofurantoin, sulfamethoxazole-trimethoprim, ciprofloxacin, isoniazid), newer agents of anti-neoplastic therapy (such as tyrosine kinase inhibitors and immune checkpoint inhibitors), and drugs to treat autoimmune disorders (TNF alpha inhibitors) (4). Currently, DILI remains a diagnosis of exclusion, depending on liver function tests (aminotransferases ALT and AST, bilirubin levels and alkaline phosphatase) and causality scores (for instance, the Roussel-Uclaf Causality Assessment Method score) to detect and classify liver damage (5). The following thresholds for a diagnosis of DILI were suggested by an international expert working group and are in use: ALT value ≥5× ULN, ALP value ≥2× ULN or ALT value ≥3× ULN and TB ≥2× ULN (6). New biomarkers that can indicate immune activation accompanying the rise in liver function tests secondary to DILI, will likely soon constitute the clinical application of precision medicine in this area (7, 8).

Since causality of the drug in question can be difficult to ascertain in cases of idiosyncratic DILI, considerable emphasis has been placed on generating data and formulating large national registries. The first DILI registry was set up in Spain, in 1994 (9); the Drug Induced Liver Injury Network (DILIN) in the US came into action in 2004, and funded by the National Institutes of Health (NIH) began the process of prospectively analyzing data from twelve different sites in the country (4). Other registries have been formed in countries and across continents, providing means for effective collaboration amongst healthcare practitioners dealing with DILI, and corroboration of data; these include China, India, Korea and Europe (9). This practice is crucial to understanding the patterns of drug usage and DILI in the context of local population and health practice, setting up archives that can propel further clinical and translational research.

Pakistan does not have a nationwide registry for DILI, effectively hindering any data analysis to provide numbers on incidence and prevalence of DILI in a country with an abundance of viral hepatitis, hepatocellular carcinoma, and fatty liver disease, among other liver diseases. The aim of this project is to first collect retrospective data at our tertiary care center, and then partner with other private and public sector hospitals in the region to centralize this data, with the ultimate goal of establishing a national DILI network, in full collaboration with government, pharmaceutical industries and private healthcare facilities.

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